Renal anemia, an important complication of chronic kidney disease (CKD), has been reported to have a major effect on the occurrence of cardiovascular events [1]. For the treatment of renal anemia, erythropoietin (EPO), an erythropoiesis-stimulating agent (ESA), is typically administered. However, in Japan, there are patients who exhibit ESA-resistant anemia, in whom EPO administration does not improve the condition. Hosokawa et al. [2] reported that zinc deficiency may be a cause of ESA-resistant anemia because serum zinc concentrations are low in maintenance dialysis patients.

Mahajan et al. [3] reported that zinc deficiency is caused by impaired absorption of zinc from the intestinal tract, accompanied by decreased renal function. A relatively low zinc intake may also be involved due to adherence to a low-protein diet, which is commonly prescribed as a dietary intervention for patients with renal failure. In nephrotic syndrome, serum albumin levels decrease as the amount of protein lost into the urine increases, which also lowers the level of protein-bound zinc.

Alternatively, zinc deficiency may occur due to an increased concentration of zinc bound to amino acids, which is excreted in urine. It has been reported that in patients with diabetic nephropathy presenting with proteinuria, serum zinc concentrations are lower than those in healthy people as well as patients with diabetic nephropathy without proteinuria [4, 5].

Zinc is a microelement vital to the functioning of the human body because it is a constituent of more than 500 enzymes, including DNA repair enzymes, inflammatory mediators, growth factors, and immune response proteins. In this study, we aimed to determine the frequency of serum zinc deficiency at each CKD stage and evaluate the effects of zinc acetate dihydrate (Nobelzin®) on hypozincemia, taste disturbances, and anemia.

Effect of Zinc Acetate Dihydrate (Nobelzin®) Treatment on Anemia and Taste Disorders in Patients with Chronic Kidney Disease with Hypozincemia


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Some patients with chronic kidney disease (CKD) receiving hemodialysis develop erythropoietin-resistant anemia, possibly due to zinc deficiency. The frequency of zinc deficiency in CKD (stages 1-5 and 5D) and CKD improvement via zinc supplementation are not completely verified. Here 500 CKD patients (Stage 1/2, n = 100; Stage 3, n = 100; Stage 4, n = 100, Stage n = 5, 100; Stage 5D, n = 100) will be recruited to determine the frequency of serum zinc deficiency at each CKD stage. Patients with serum zinc concentrations < 80 μg/dL will be treated with zinc acetate dihydrate (Nobelzin®) to evaluate its effects on hypozincemia, taste disturbances, and anemia.

Key words: zinc acetate dihydrate, anemia, chronic kidney disease

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300 enzymes and is involved in cell division, nucleic acid metabolism, and more; it is also involved in the synthesis and release of insulin from pancreatic β-cells [6]. Zinc deficiency in vivo causes symptoms such as developmental disorders, anemia, immune deficiency, gonadal dysfunction, dermatological conditions (dermatitis and hair loss), anorexia, and taste disorders [7].

Polaprezinc (Promac<sup>®</sup>), an antiulcer drug, has been used as a therapeutic agent for hypozincemia because it contains zinc, but this is an off-label use. In recent years, the indication of zinc acetate dehydrate (Nobelzin<sup>®</sup>), a drug for the treatment of Wilson’s disease, has extended to the treatment of hypozincemia. In this study, we will conduct cross-sectional verification to determine the frequency of hypozincemia in patients withCKD, and the clinical factors associated with this condition. In addition, for CKD patients who are zinc-deficient, the effect of zinc acetate dihydrate supplementation on anemia and taste disorders will be examined in a prospective intervention trial. The aim of this study is to establish a therapeutic strategy for the broad range of clinical symptoms associated with hypozincemia in patients with CKD.

### Endpoints

The primary evaluation items in the intervention trial with zinc acetate dihydrate supplementation are the improvement in the patients’ serum zinc concentrations and zinc deficiency-related symptoms compared with those before the treatment. The secondary evaluation items are improvement effects on the patients’ blood hemoglobin and serum alkaline phosphatase concentrations compared with those before the treatment.

### Eligibility Criteria

To participate in the study, patients will be required to fulfill the following criteria: (1) having chronic kidney disease, (2) aged 20-90 years, and (3) having provided written consent to participate in the study. The exclusion criteria are as follows: (1) deemed unsuitable for enrollment by the investigator, e.g., patients with chronic liver failure, chronic inflammatory bowel disease, extreme malnutrition or poor oral intake, and (2) taking polaprezinc or dietary supplements. The inclusion criteria for the zinc supplement administration are a serum zinc concentration < 80 μg/dL and showing either zinc deficiency symptoms or anemia. The study enrollment period is planned from November 2017 to March 2019.

### Treatment Methods

#### Study design.

Study participants will be patients diagnosed with CKD who are being treated on an outpatient basis at Juntendo University Hospital, Tokyo, Japan. A cross-sectional study will be conducted to determine the frequency of hypozincemia at each CKD stage (stages 1-5 and 5D). We will also examine the relationship between the patients’ serum zinc concentration and various clinical and laboratory findings: age, comorbid diabetes, estimated glomerular filtration rate (eGFR), presence of proteinuria, and laboratory values for hemoglobin, serum albumin, serum uric acid, serum alkaline phosphatase, iron, ferritin, and copper.

After their examinations, patients with serum zinc concentrations < 80 μg/dL will be requested to complete a questionnaire on symptoms experienced; these symptoms (taste disorders, anorexia, dermatological symptoms, or stomatitis) may be related to zinc deficiency (Table 1-1). Thereafter, zinc acetate dihydrate will be administered for 24 weeks starting at an initial daily dose of 50 mg (Fig. 1). Blood samples will, as far as possible, be collected on a monthly basis. If there is no improvement in a patient’s serum zinc concentration, the dosage may be increased up to a maximum of 250 mg/day. At the end of the treatment period, patients will complete the questionnaire again, and final blood and urine samples will be collected (Table 1-2).

#### Table 1-1 Questionnaire on zinc deficiency symptoms (pre-survey)*

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Currently, do you have a taste disorder such as not being able to</td>
<td>taste or feeling the same taste for whatever you eat?</td>
</tr>
<tr>
<td>taste or feeling the same taste for whatever you eat?</td>
<td>0: No, 1: A little, 2: Yes</td>
</tr>
<tr>
<td>2. Please tell me whether there are the following symptoms that may be</td>
<td>related to zinc deficiency.</td>
</tr>
<tr>
<td>related to zinc deficiency.</td>
<td>1) Stomatitis</td>
</tr>
<tr>
<td>1) Stomatitis</td>
<td>0: Not at all, 1: Almost never, 2: Sometimes, 3: Frequently</td>
</tr>
<tr>
<td>2) Prone to skin troubles (contused wound and itching)</td>
<td>0: Not at all, 1: Almost never, 2: Sometimes, 3: Frequently</td>
</tr>
<tr>
<td>3) Anorexia</td>
<td>0: No, 1: A little, 2: Yes</td>
</tr>
</tbody>
</table>

*If the patient has a symptom even to a slight degree, select 1, 2, or 3.
Interventions. If transferrin saturation at the start of treatment is ≤ 20% and ferritin levels are ≤ 100 ng/mL, iron will be supplemented until a recommended value if tolerated. Nonetheless, zinc acetate dihydrate will be supplemented until anemia persists only if the patient can receive zinc acetate dihydrate treatment despite poor tolerance to iron treatment. If a patient’s hemoglobin levels are > 12 g/dL during the treatment, EPO administration will be reduced by half. Zinc acetate dihydrate, starting from 50 mg/day, will be administered to the patients with serum zinc concentrations < 80 μg/dL. After 4 weeks of administration, if the serum zinc concentration has not reached 80 μg/dL, the dose will be increased by 25 mg/day. Zinc acetate dihydrate may be increased up to a daily maximum of 250 mg, as needed. The serum zinc target level is set at approx. 80-130 μg/dL. In cases in which the patient’s serum zinc concentration rises above 250 μg/dL, the dose will be reduced by half [8]. If the dose reduction fails to bring the serum zinc concentration below 250 μg/dL, the medication will be stopped.

Should a copper or iron deficiency be observed during treatment, the administration of zinc acetate dihydrate will be reduced or stopped, or the supplementation of copper or iron will be initiated. Close attention will be paid to copper deficiency when the patient’s serum zinc concentration is > 200 μg/dL or the serum copper concentration is around 20-30 g/dL [8].

Ethical considerations. This research protocol has been approved by the Institutional Review Board of Juntendo University Hospital. The study will be conducted in compliance with the Declaration of Helsinki in conjunction with our hospital’s Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study is registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN 000031655).

Statistical Considerations

Sample size. Considering that few patients present with anemia, the frequency of hypozincemia is also assumed to be low in patients with Stage 1/2 CKD. According to the Third National Health and Nutrition Examination Survey (NHANES) in the United States, the frequency of anemia at each CKD stage was Stage 3: 9%, Stage 4: 33%, and Stage 5: 67% [9]. Considering that the consent to intervention cannot be obtained without clear zinc deficiency symptoms and that the relationship between the serum zinc concentration and clinical features will be examined in this cross-sectional study, we estimated that a total of 500 participants will be needed.

Statistical analysis. We will analyze continuous variables for each CKD stage by performing an analysis of variance (ANOVA), and the association between the serum zinc concentration and associated clinical features will be assessed by Spearman’s correlation coefficient. In addition, changes from before to after zinc supplement treatment will be analyzed by a paired t-test. A p-value < 0.05 will be accepted as significant. The statistical analysis will be performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).
References


